IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. Plovin 1-A
Wolfgang HEIL et al.	:	Examiner: S. Hui
Serial No.: 09/654,227	:	Group Art Unit: 1617
Filed: August 31, 2000	:	

For: PHARMACEUTICAL COMPOSITION FOR USE AS A CONTRACEPTIVE

DECLARATION UNDER 37 C.F.R. §1.132

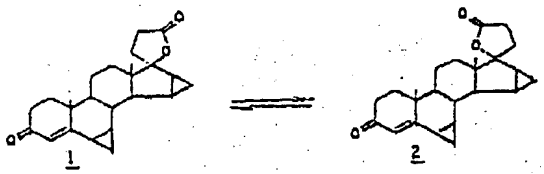
SIR:

I, Dr. Adrian Funke, being duly warned, declare that:

1. My C.V. is attached. I am a member of the Pharmaceutical Development Department of Schering AG, the assignee of the above-identified application. My direct supervisor reports to Dr. Ralph Lipp, a named inventor on this application.

2. I have read and understood the above-identified application, the article of Nickisch et al., Tetrahedron Letters, vol. 27, no. 45, pp. 5463-5466 (1986) (Nickisch), USP 5,534,270 to DeCastro, and the office action of March 23, 2004.

3. Nickisch describes acid catalyzed rearrangements of 15β,16β-substituted-17α-pregnene-21,17-carbolactone derivatives. Of particular interest is the disclosed isomerization of drospirenone (1) to the isoform (2):



1 2

4. Nickisch incubated drospirenone for 3 hours with 0.1 N hydrochloric acid at room temperature. At the end of this incubation, drospirenone and the isoform were found in a 2:8 ratio, i.e., with the iso-form dominant (80%). Nickisch also performed a second experiment, incubating the isoform for 3 hours with 0.1 N hydrochloric acid at room temperature. At the end of this second incubation experiment, drospirenone and the isoform were also found in the same 2:8 ratio. Nickisch concludes that the 2:8 ratio thus represents the thermodynamic equilibrium of the isomerization/rearrangement. This shows that the isomerization reaction is even faster than indicated by the result of an 80% isomerization of drospirenone within 3 hours at room temperature, since 3 hours are enough even to reach the equilibrium point.

5. One of ordinary skill in the art would be aware of the well-known dependency of reaction kinetics on temperature and the general rule that chemical reactions are typically accelerated by a factor of 2 – 3 upon a temperature increase of 10°C. This is confirmed, for example, by the attached publication on temperature dependency of reaction kinetics of Martin/Swarbrick/Cammarata, Physikalische Pharmazie, Chapter 8.5.1, p. 219, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart (1987) (translation attached).

6. One of ordinary skill in the art would also be aware of the well known facts that typical pH-values of the human stomach are pH 1 – 3 in the fasted state and up to pH 6 in the fed state, and typical residence times are half lives of solutions in the stomach of 10 – 50 minutes, and half lives of non-disintegrating tablets in the stomach of 0.5 – 7 hours. (Bauer/Frömming/Führer, Pharmazeutische Technologie, Chapter 7 on Biopharmacy, Section 2.1.2, p.188, Georg Thieme Verlag, Stuttgart - New York (1993)) (translation attached).

7. The conditions used in the Nickisch experiments are directly comparable with physiological conditions in the human stomach and would be considered by one of ordinary skill in the art to be representative of what would be expected to happen in the human stomach, i.e., in this case, rapid isomerization of drospirenone would be expected to occur.

8. Nickisch's experiments are performed in 0.1 N hydrochloric acid. (This means here 0.1 mole/liter, i.e., a pH of 1.) The acidic principle in the human stomach is also

hydrochloric acid. Thus, a situation where the human stomach has a pH for example of 1 directly correlates to Nickisch's acidic test conditions. That the Nickisch experiment was performed in a controlled in vitro environment having a single aliquot of acid whereas the stomach provides an in vivo environment with a replenishing acid supply and more varying conditions, would not change the expectation of one of ordinary skill for a rapid isomerization of drospirenone in the stomach. The reaction per se would not affect the pH in either circumstance. (The reaction does not consume the acid catalyst.) As the stomach conditions change, of course, the isomerization degree may change to the extent the pH values are affected.

9. The temperature in the human stomach of course is about 37°C (body temperature), i.e. at least 10°C higher than in Nickisch's test (assuming room temperature to be 20 – 25°C). Thus, the isomerization reaction in a human stomach at pH 1 would in general be expected to be accelerated by a factor on the order of 2 – 3 when compared to Nickisch's test. The higher temperature in the stomach would thus lead one of ordinary skill in the art to conclude that the isomerization would occur even more rapidly in the stomach than it did in Nickisch's experiment where it was complete within 3 hours or less.

10. As can be seen, the lower pH's of a typical human stomach are comparable to that employed in Nickisch's experiments and the typical human temperatures are similarly comparable and, indeed, would lead to an even faster isomerization. Thus, a skilled worker designing an oral administration form for drospirenone would find Nickisch to establish a high likelihood that drospirenone would be isomerized rapidly and to a significant extent during its residence in the stomach. The fact that there is a wide variation in typical residence times (half lives) of solutions or non-disintegrating tablets in the stomach (see paragraph 6 above), would not affect the significance of this Nickisch teaching to one of ordinary skill in the art. This is also true with regard to the wide variation in possible pH values depending on fasted/fed circumstances, as also discussed in paragraph 6 above. This is because one of ordinary skill in the art developing an oral dosage form has the task to provide a form which works well for all patients under all circumstances. Thus, he or she has to consider a worst case scenario, i.e. low pH and long residence time. Any person of ordinary skill in the art

would have expected that, in a worst case scenario, the isomerization reaction will reach the thermodynamic equilibrium of only 20% drospirenone during the stomach passage. Even in a perhaps more favorable scenario assuming medium pH (e.g. 1.5-2) and medium residence time (e.g. 2-3 hours), extensive isomerization would be expected by any person skilled in the art.

11. Furthermore, Nickisch states in its second sentence on its first page that "virtually all" changes of the 17-spiro-5-ring-lactone result in a reduction of the antimineral-corticoidal action. As can be seen from the schematic depiction of the isomerization reaction in paragraph 3 above, the involved isomerization occurs precisely in this 5-membered lactone ring of drospirenone. Thus, Nickisch not only teaches a skilled worker to expect complete equilibrium (80%) isomerization of drospirenone or at least extensive isomerization thereof upon passage through the stomach, but also that the resultant isomerization will change the pharmacological activity of drospirenone, at least by reducing its antimineral-corticoidal action, which is reported for virtually all changes in the 5-membered lactone ring. Thus, Nickisch et al. would be viewed by any person of ordinary skill as teaching away from administering drospirenone in a form in which it will be exposed to the stomach environment.

12. I understand that the examiner is alleging it would have been obvious to formulate drospirenone for oral administration in micronized form. (3rd paragraph of page 6 of the office action). The examiner reasons that motivation to employ the micronized form of drospirenone comes from DeCastro who "teaches a method of preparing very small drug particles, less than 400 nm, for poorly soluble drugs such as steroids in order to increase the bioavailability of the drug;" and "Possessing the teaching of DeCastro, one of ordinary skill in the art would have optimized the particle size of the herein claimed compounds to increase the bioavailability of the same;" and "Furthermore, the herein recited physical characteristics of the herein claimed compounds would have been seen as either the routine optimization of the effect parameters or the result of the reducing of particle size of the drospirenone using DeCastro's method." Thus, the examiner seems to argue that DeCastro teaches micronization straightforwardly leads to increased bioavailability for steroid drugs by particle size reduction. However, this clearly cannot be applicable to drospirenone.

13. DeCastro teaches at column 1, lines 28-30: "It is know[n] that the rate of dissolution of a particular drug can increase with increasing surface area, i.e., decreasing particle size." But Nickisch teaches that an increased exposure to the environment of the stomach, which would occur upon an increase in the rate of dissolution of drospirenone, will lead to an enhancement of the deleterious isomerization of drospirenone. Thus, DeCastro's statement that increased rates of dissolution can be the result produced by micronization would strongly lead a skilled worker away from micronizing drospirenone.

14 In conclusion, Nickisch teaches away from exposure of drospirenone to the environment of the stomach. To the extent micronization is alleged to increase the rate of dissolution of drospirenone, a skilled worker is taught not to micronize drospirenone or, at the very least, is not motivated to micronize drospirenone, or to formulate it in any other rapid dissolution form for oral administration.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 19.05.2004 Signed: Funke

Dr. Adrian Funke

Curriculum Vitae for Dr. Adrian Funke

Born: 13 January 1972 in Trier, Germany
German citizen
Married, two children

Basic studies

1978-91	Elementary and high school
May 1991	High school Graduate

Higher education

1991-95	Pharmacy studies, Free University of Berlin
1995-96	Practical studies in Schering AG, Berlin
1996	Practical studies in Pharmacy in Berlin
Nov 1996	Pharmacist Graduate

Military service

Jan-Oct 1997	Basic military service as a Pharmacist

Postgraduate education

1996-2000	Associate Lecturer, Pharmaceutical Chemistry and Pharmaceutical Technology, Free University of Berlin
1998-2000	Postgraduate Pharmaceutical Technology studies, Free University of Berlin and Pharmaceutical Development, Schering AG
Sept 2000	Graduation as Doctor in Natural Science at the Free University of Berlin under the guidance of Prof. Dr. R. H. Müller

Professional Experience

Oct 2000 to present	Leader of the scientific work group "Oral Dosage Forms Development" at Schering AG

Professional memberships

Member of the German Pharmaceutical Society
Member of the International Association for Pharmaceutical Technology

List of publications

Posters and lectures

1. A. P. Funke, C Günther, R. H. Müller, and R. Lipp, *Low-frequency sonophoresis of methyl nicotine at physiological skin temperature*, Poster, 3rd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin (Germany) 03.-06.04.2000.

2. A. P. Funke, H N. Petry, T. Backensfeld, and R. Lipp, *Use of the Caco-2 model to predict intestinal absorption of class III-IV drugs from different formulations*, Lecture, Annual Meeting of the Deutsche Pharmazeutische Gesellschaft (German Pharmaceutical Society), Berlin (Germany), 09.-12 10.2002; Arch. Pharm. Pharm. Med. Chem., 335, Suppl. 1, 59 (2002).

3. H N. Petry, P. Lienau, and A P. Funke, *In-vitro absorption and metabolism of estradiol in the Caco-2 model and the effects of formulations*, Poster, Annual Meeting of the Deutsche Pharmazeutische Gesellschaft (German Pharmaceutical Society), Berlin (Germany), 09.-12.10.2002; Arch. Pharm. Pharm. Med. Chem., 335, Suppl. 1, 118 (2002).

4 R. Schiller, H. W. Motzkus, A. P. Funke, C. Günther, and R. Lipp, *DSC measurements on full thickness mice skin – a way to evaluate the mechanism of permeation enhancement of highly lipophilic drugs*, Poster, 7th International Conference / Workshop on Pharmacy and Applied Physical Chemistry, Innsbruck (Austria), 07.-11.09.2003.

Printed publications

1. A. P. Funke, *Transdermale Absorption von hoch lipophilen, basischen Antiestrogenen aus Flüssigformulierungen und Matrix-Transdermalsystemen*, PhD thesis, Freie Universitat Berlin, Berlin (Germany), 2000.

2. A. Funke, R. Lipp und C Günther, *Compositions for use as penetration inhibitors in transdermal formulations for highly lipophilic active ingredients*, Int. patent application, WO0176608 (18 10.2001).

3. A. P. Funke, R. Schiller, H. W. Motzkus, C. Günther, R. H. Müller and R. Lipp, *Transdermal delivery of highly lipophilic drugs: in vitro fluxes of antiestrogens, permeation enhancers, and solvents from liquid formulations*, Pharm. Res., 19(5), 661-668 (2002).

4. A. P. Funke, C. Gunther, R. H. Müller, and R. Lipp. *In-vitro release and transdermal fluxes of a highly lipophilic drug and of enhancers from matrix TDS*, J. Control. Rel., 82, 63-70 (2002).

5. A. P. Funke, C. Günther, R. H. Müller, and R. Lipp, *Development of matrix patches for transdermal delivery of a highly lipophilic antiestrogen*, Drug. Dev. Ind. Pharm., 29(7), 785-793 (2003).